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Performance of the BioPlex 2200 HIV Ag-Ab assay for identifying acute HIV infection

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Author roles: All authors meet the journal's criteria for authorship. Individual contributions/author roles are listed below.

Susan H. Eshleman	Designed the study; drafted the manuscript
Estelle Piwowar-Manning	Designed the study; analyzed data
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Barbara Debevec	Performed testing
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Abstract

Background—Assays that detect HIV antigen (Ag) and antibody (Ab) can be used to screen for HIV infection.

Objectives—To compare the performance of the BioPlex 2200 HIV Ag-Ab assay and two other Ag/Ab combination assays for detection of acute HIV infection.

Study Design—Samples were obtained from 24 individuals (18 from the US, 6 from South Africa); these individuals were classified as having acute infection based on the following criteria: positive qualitative RNA assay; two negative rapid tests; negative discriminatory test. The samples were tested with the BioPlex assay, the ARCHITECT HIV Ag/Ab Combo test, the Bio-Rad GS HIV Combo Ag-Ab EIA test, and a viral load assay.

Results—Twelve (50.0%) of 24 samples had RNA detected only (>40 to 13,476 copies/mL). Ten (43.5%) samples had reactive results with all three Ag/Ab assays, one sample was reactive with the ARCHITECT and Bio-Rad assays, and one sample was reactive with the Bio-Rad and BioPlex assays. The 11 samples that were reactive with the BioPlex assay had viral loads from 83,010 to

>750,000 copies/mL; 9/11 samples were classified as Ag positive/Ab negative by the BioPlex assay.

Conclusions—Detection of acute HIV infection was similar for the BioPlex assay and two other Ag/Ab assays. All three tests were less sensitive than a qualitative RNA assay and only detected HIV Ag when the viral load was high. The BioPlex assay detected acute infection in about half of the cases, and identified most of those infections as Ag positive/Ab negative.

Keywords

HIV; acute; Ag/Ab assay; BioPlex

BACKGROUND

Screening for HIV infection can be performed with assays that detect HIV antibody (Ab) only (3rd generation assays) or with combination assays that detect HIV antigen (Ag) and Ab [1, 2]. The ability to detect HIV Ag in addition to Ab can shorten the window period for detection of HIV infection [3, 4]. Assays that provide one test result for Ag and/or Ab are often referred to as 4th generation assays. These assays can detect acute (Ag-positive/Ab-negative) HIV infections [5]. Some Ag/Ab assays provide separate test results for HIV Ag and Ab [3]; these assays have the potential to identify acute infections.

In 2015, the United States (US) Food and Drug Administration (FDA) approved use of the BioPlex 2200 HIV Ag-Ab (BioPlex) assay for HIV testing [6]. BioPlex is an automated, multiplex flow immunoassay that provides separate results for detection of HIV-1 p24 Ag, HIV-1 Ab (groups M and O), and HIV-2 Ab [7]. Previous reports indicate that the overall sensitivity and specificity of the BioPlex assay are similar to other Ag/Ab assays [8–10]. Those studies included relatively few acute HIV infection samples (range: 4-13 samples) [8–10]. This study evaluated the ability of the BioPlex assay to detect and identify acute infections.

OBJECTIVES

To evaluate the performance of the BioPlex assay for detection and identification of acute HIV infection.

STUDY DESIGN

Retrospective testing was performed using pre-seroconversion plasma samples from participants in the HIVNET 015 (EXPLORE) study (samples from the US) [11, 12] and the HPTN 067 (ADAPT) study (US and South Africa). HIVNET 015 was a vaccine preparedness study. HPTN 067 evaluated use of tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) for pre-exposure prophylaxis (PrEP) [13, 14]. Samples were initially tested with two HIV rapid tests (Oraquick Advance Rapid HIV-1/2 Antibody Test, Orasure Technologies, Bethlehem, PA; Uni-Gold Recombigen HIV-1/2, Trinity Biotech PLC, Bray, Ireland), an HIV discriminatory test (Geenius HIV 1/2 Supplemental Assay, Bio-Rad Laboratories, Redmond, WA), and a qualitative HIV RNA assay (Aptima HIV-1 RNA

Qualitative Assay, Hologic Gen-Probe, San Diego, CA); limit of detection: 30 copies/mL). Acute infection was defined by detection of HIV RNA in samples that had two non-reactive rapid tests and a negative discriminatory test. Samples classified as acute infections were tested with three Ag/Ab assays: the ARCHITECT HIV Ag/Ab Combo test (ARCHITECT Combo; Abbott Laboratories, Abbott Park, IL), the GS HIV Combo Ag-Ab EIA test (Bio-Rad Combo), and the BioPlex 2200 HIV Ag-Ab assay (BioPlex; Bio-Rad Laboratories). HIV viral load testing was performed using RealTime HIV-1 Viral Load assay (Abbott Molecular, Des Plaines, IL); samples with limited plasma volume were tested with a validated dilution version of this assay with a limit of detection of 400 copies/mL HIV RNA. The Ag/Ab assays determine reactivity based on a signal-to-cutoff ratio (S/CO, ARCHITECT Combo and Bio-Rad Combo) or Index Value (BioPlex). The BioPlex package insert indicates that index values are not correlated with HIV viral load [7].

RESULTS

Samples were analyzed from 24 individuals with acute infection (US [n=18], South Africa [n=6]). All 24 samples had non-reactive HIV rapid tests, a negative HIV discriminatory test, and a positive qualitative HIV RNA test (Table). The samples were also tested with three Ag/Ab assays (ARCHITECT Combo, Bio-Rad Combo, BioPlex) and a viral load assay. Twelve (50.0%) samples had non-reactive results with all three Ag/Ab assays. Three of the 12 samples were positive with the qualitative HIV RNA assay only (viral load <400 copies/mL); the remaining nine were positive with both the qualitative HIV RNA assay and a viral load assay (median viral load: 2,917 copies/mL; range: 400 to 13,476).

The remaining 12 (50.0%) samples were positive with both HIV RNA assays and had reactive results with at least two of the three Ag/Ab assays. This included: 10 that were reactive with all three Ag/Ab assays (median viral load: >750,000; range: 176,185 to >750,000), one that was reactive with the Abbott Combo and Bio-Rad Combo assays only (viral load: 125,848 copies/mL), and one that was reactive with the Bio-Rad Combo assay and the BioPlex assay only (viral load: 83,010 copies/mL). Among the 11 (45.8%) samples that had a reactive BioPlex result, two had both Ag and Ab detected (viral load: >750,000 copies/mL) and nine had Ag detected only (median viral load: 662,217 copies/mL; range: 83,010 to >750,000). For all three assays, there was no correlation between the S/CO or Index Values and viral load in this set of acute infection samples (Supplementary Figure).

CONCLUSIONS

In this study, detection of acute HIV infection was similar for the BioPlex, ARCHITECT Combo, and Bio-Rad Combo assays. The BioPlex assay was reactive for 11 (45.8%) of 24 acute infection samples, and identified 9 (39%) of the samples as Ag positive/Ab negative. All three Ag/Ab assays were less sensitive than a qualitative HIV RNA assay, and only detected HIV Ag when the HIV viral load was high (samples reactive with all three assays had viral loads >170,000 copies/mL). The US Centers for Disease Control recommends use of an Ag/Ab assay for HIV screening. If the Ag/Ab assay is non-reactive, no further testing is needed [2]. This algorithm would have missed about half of the acute infections in this study. There is currently only one other FDA-approved HIV Ag/Ab assay that reports

separate results for Ag and Ab detection (the Alere Determine HIV-1/2 Combo rapid test, Alere, Scarborough, ME) [6]. That test is more sensitive than 3rd generation screening assays for detecting acute infection, but less sensitive than laboratory-based Ag/Ab assays [15, 16]. HIV RNA testing is currently the most sensitive method for detection of acute HIV infection. However, use of individual HIV RNA assays to screen for acute infections is costly. Pooled HIV RNA assays offer a less costly method for detecting acute HIV infection, but are less sensitive, more complex, and more labor-intensive than individual HIV RNA assays [17].

Previous studies have shown that HIV subtype may affect the performance of some HIV screening assays [18, 19]. A limitation of the study was that the sample set included only six acute infection samples from subtype C endemic areas. The sample set also included only two samples with HIV viral loads between 10,000 and 100,000 copies/mL. Analysis of a larger set of acute infection samples in this viral load range is needed to determine the amount of virus needed for detection of acute infection with each assay.

This study included eight samples from a PrEP trial [13, 14]. Only three of the eight infections were detected by Ag/Ab tests (Cases 2, 5, and 12). Four (50.0%) of the eight samples had viral loads ≤400 copies/mL, compared to none of the 16 samples from the HIVNET 015 study, which was performed before PrEP was in use. Two of the four participants with low viral loads were infected at study enrollment (prior to PrEP administration); one was infected prior to study randomization after receiving once-weekly, directly-observed TDF/FTC; and one was randomized to an event-driven PrEP regimen, but had no study drug detected in the months preceding the acute infection visit. Therefore, it is unlikely that PrEP use was the cause of viral suppression in these cases.

In this study, the BioPlex assay, ARCHITECT Combo assay, and Bio-Rad Combo assay each detected about one half of the acute infections. The BioPlex assay identified 9 (39%) of the 23 samples as Ag positive/Ab negative infections. Additional information is needed to determine whether detection of Ab by the BioPlex assay in the two remaining samples reflects more sensitive detection of Ab by this assay, or a false positive Ab result.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- The BioPlex assay and two other Ag/Ab assays had similar sensitivity for detecting acute infection.
- HIV RNA assays were more sensitive than Ag/Ab assays for detecting acute infection.
- HIV Ag was only detected by the BioPlex assay when the HIV viral load was high.

Table

HIV test results from individuals with acute infection.

#[a]	Rapids 1/2[b]	Abbott (S/CO)[c]	Bio-Rad (S/CO)[c]	BioPlex (IDX)[c]	Discr. Geenius	Viral load (c/mL)	HIV RNA Aptima
1	NR/NR	**R (32.7)**	**R (11.8)**	**R (Ag:2.8, Ab:58.1)**	Neg	**>750,000**	**R**
2*	NR/NR	**R (25.0)**	**R (12)**	**R (Ag:2.1, Ab:13.6)**	Neg	**>750,000**	**R**
3	NR/NR	**R (172.0)**	**R (max)**	**R (Ag:39.0)**	Neg	**>750,000**	**R**
4	NR/NR	**R (7.7)**	**R (3.8)**	**R (Ag:16.7)**	Neg	**>750,000**	**R**
5*	NR/NR	**R (45.0)**	**R (13)**	**R (Ag:13.6)**	Neg	**>750,000**	**R**
6	NR/NR	**R (15.4)**	**R (10.1)**	**R (Ag:10.2)**	Neg	**675,514**	**R**
7	NR/NR	**R (13.2)**	**R (2.7)**	**R (Ag:12.7)**	Neg	**662,217**	**R**
8	NR/NR	**R (11.6)**	**R (10.2)**	**R (Ag:14.2)**	Neg	**377,329**	**R**
9	NR/NR	**R (20.7)**	**R (6.8)**	**R (Ag:1.5)**	Neg	**358,470**	**R**
10	NR/NR	**R (6.6)**	**R (3.0)**	**R (Ag:13.8)**	Neg	**176,185**	**R**
11	NR/NR	**R (3.5)**	**R (2.2)**	NR	^ Neg	**125,848**	**R**
12*	NR/NR	NR	**R (1.3)**	**R (Ag:1.4)**	Neg	**83,010**	**R**
13	NR/NR	NR	NR	NR	Neg	**13,476**	**R**
14	NR/NR	NR	NR	NR	Neg	**8,533**	**R**
15	NR/NR	NR	NR	NR	Neg	**3,984**	**R**
16	NR/NR	NR	NR	NR	Neg	**3,167**	**R**
17	NR/NR	NR	NR	NR	Neg	**2,917**	**R**
18*	NR/NR	NR	NR	NR	Neg	**2,100**	**R**
19	NR/NR	NR	NR	NR	Neg	**790**	**R**
20	NR/NR	NR	NR	NR	Neg	**724**	**R**
21*	NR/NR	NR	NR	NR	Neg	**400**	**R**
22*	NR/NR	NR	NR	NR	Neg	<400	**R**
23*	NR/NR	NR	NR	NR	Neg	<400	**R**
24*	NR/NR	NR	NR	NR	Neg	<400	**R**

Abbreviations: gen: generation; S/CO: signal-to-cutoff ratio; IDX: index value; Discr.: discriminatory; c/mL: copies per mL; R: reactive; Ag: antigen; Ab: antibody; NR: non-reactive. Reactive/positive results are shown in bold font.

[a]The eight samples marked with an asterisk were from the HPTN 067 PrEP trial. Six samples were from South Africa (samples 5, 12, 18, 21, 23, and 24), and two samples were from the United States (samples 2 and 22). Acute infection was documented at enrollment (prior to PrEP administration) in two cases (samples 21 and 22); during or immediately after directly observed, once-weekly PrEP in two cases (samples 5 and 23); and after study randomization in the remaining four cases (samples 2, 12, 18 and 24). Tenofovir was detected at high levels in the acute infection sample from one participant randomized to a time-driven regimen (sample 18); tenofovir was not detected in the acute infection samples from the other three randomized participants [14].

[b]Two FDA-approved 3rd generation HIV rapid tests were used for testing (Oraquick Advance Rapid HIV-1/2 Antibody Test and Uni-Gold Recombigen HIV-1/2).

[c]Three FDA-approved Ag/Ab assays were used for testing (ARCHITECT HIV Ag/Ab Combo test; GS HIV Combo Ag-Ab EIA test; BioPlex 2200 HIV Ag-Ab assay). For all three assays, a signal-to-cutoff or Index Value ≥1 is considered reactive.